Comments on the Synthesis of Aminomethylphosphonic Acid

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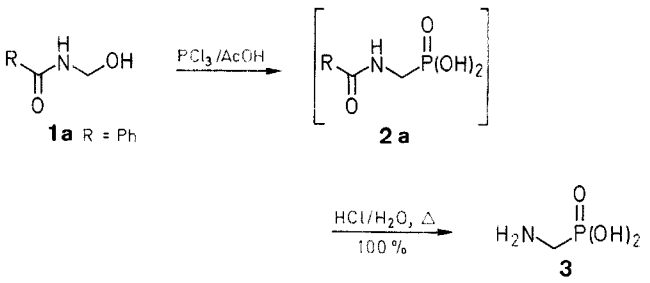
Two simple methods for the synthesis of aminomethylphosphonic acid from phosphorus(III) chloride and 1,3,5-triacylhexahydro-1,3,5-triazine or *N*-(hydroxymethyl)benzamide are described.

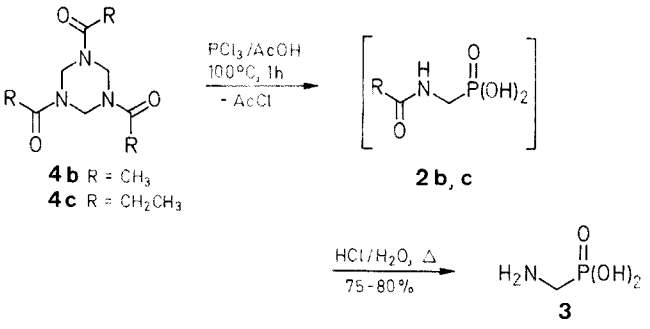
The simplest aminoalkylphosphonic acid, i.e., aminomethylphosphonic acid, is the subject of hundreds of literature reports, most of them being somehow connected with *N*-phosphonomethylglycine (Glyphosate), an active ingredient of Roundup, a well known herbicide.[1-3] Aminomethylphosphonic acid (AMPA) is both, a metabolite of Glyphosate and a useful synthon for its production (for example, Refs. 4–7). The recently reported synthesis of aminomethylphosphonic acid by reaction of *N*-(hydroxymethyl)benzamide with phosphorus(III) chloride and trimethyl phosphite followed by acidic hydrolysis,[8] prompts us to give some comments on the preparation of this acid and to present two modified procedures.

In two patents,[12,13] which were the first reports on aminomethylphosphonic acid (**3**), the synthesis of this acid by reaction of phosphorus(III) chloride with *N*-(hydroxymethyl)carboxamides **1** and then with acetic acid was described.

The 100% overall yield claimed in Ref. 13 was repeatedly questioned later.[8,14] However, we have found that this method, in a slightly modified form, is still the most convenient preparation of aminomethylphosphonic acid. Reports on the application of this probably well known method to the synthesis of aminomethanephosphonic acid or derivatives thereof have only been published in patents.[15-20] Useful modifications of the method were also claimed in two patents.[18,19] The original procedure[12,13] could not be improved by using simple aliphatic *N*-(hydroxymethyl)carboxamides such as *N*-(hydroxymethyl)formamide or -acetamide.[21] We have found that only aromatic *N*-(hydroxymethyl)carboxamides (e.g., **1a**) gave satisfactory results in this reaction. The reaction with several aliphatic *N*-(hydroxymethyl)carboxamides gave nitrilotris(methylphosphonic acid) as the main product and only poor yields of aminomethylphosphonic acid; this result can be rationalized on the basis of the mechanism of the amidomethylation reaction.



We also describe another simple procedure for the synthesis of aminomethylphosphonic acid by reaction of phosphorus(III) chloride (the cheapest phosphorous reagent), with the easily available 1,3,5-triacylhexahydro-1,3,5-triazines **4**. These cyclic *N*-acylaminals are obtained from nitriles and formaldehyde;[22-25] they are good amidomethylating agents and react smoothly with phosphorous acid[26] prepared *in situ* from phosphorus(III) chloride and any liquid carboxylic acid (acetic, propanoic, etc.) to give *N*-acyl derivatives **2b, c** of aminomethylphosphonic acid which can be easily deacylated to acid **3**.



It is worthy of note that non-cyclic aliphatic *N,N*-diacylaminals such as methylidenebisamides – give a mixture of products with aminomethylphosphonic acid and nitrilotris(methylphosphonic acid) as the major components in the same reaction. The mechanism of the reaction of hexahydro-1,3,5-triazines with nucleophiles is not via triazine-imine equilibrium, as it is commonly stated in the literature; according to our investigations it is an acid-catalyzed nucleophilic substitution of these cyclic aminals. Details of the mechanistic study will be published elsewhere.

Aminomethylphosphonic Acid (3):

Method A, from *N*-(Hydroxymethyl)benzamide (**1a**): Phosphorus(III) chloride (8.75 mL, 0.10 mol) is added dropwise to well stirred mixture of *N*-(hydroxymethyl)benzamide[28] (**1a**; 15.1 g, 0.10 mol) and AcOH (20 mL) at 10–25 °C. The mixture is then refluxed for 1 h, then evaporated, 8 M aqueous HCl (50 mL) is added to the residue, and this mixture is refluxed overnight. The resultant mixture is cooled to 20 °C,

benzoic acid is filtered off and washed with H_2O. The filtrate is evaporated under reduced pressure on a boiling water bath and the residue is dissolved in boiling H_2O (20 mL). Gradual addition of MeOH (100 mL) induces crystallization of product **3**. The pH of the mixture is then adjusted to 5–6 by the addition of methyloxirane or pyridine and the mixture is kept in the refrigerator overnight. The crystalline product **3** is isolated by suction, washed with MeOH, and dried at ambient temperature. The crude product (10–11 g) is recrystallized from boiling water (20 mL) by the gradual addition of MeOH (50 mL). The mixture is again stored in the refrigerator overnight. The pure product **3** is isolated by suction, washed with MeOH/H_2O (2:1) and dried 24 h; yield: 9.4 g (85%); mp 338–344°C.

Method B, from 1,3,5-Tripropanoylhexahydro-1,3,5-triazine (**4c**): Phosphorus(III) chloride (8.75 mL, 0.10 mol) is added dropwise to well stirred mixture of 1,3,5-tripropanoylhexahydro-1,3,5-triazine[22,23] (**4c**; 9.0 g, 0.035 mol) in AcOH or propanoic acid (40 mL) at 20°C. The mixture is then heated on a water bath until AcCl or propanoyl chloride has been distilled off, and then 30 min more. The oily residue is treated with 8 M aqueous HCl (50 mL) and refluxed overnight. The hydrolysate is evaporated under reduced pressure on a boiling water bath. The residue is dissolved in boiling H_2O (20 mL) and then MeOH (100 mL) is added gradually to induce crystallization of product **3**. The pH of the crystallizing mixture is adjusted to 5–6 by the addition of methyloxirane or pyridine. The resultant mixture is stored in the refrigerator overnight. The crystalline crude product **3** is isolated by suction, washed with MeOH, and dried 24 h at room temperature. This product (10–11 g) is dissolved in boiling H_2O (20 mL) and crystallization is induced by the gradual addition of MeOH (50 mL). The crystallization mixture is stored in the refrigerator overnight. The precipitated product **3** is isolated by suction, washed with MeOH/H_2O (2:1), and dried 24 h; yield: 7–8 g (75–80%); mp 335–342°C (dec) (Lit.[8] mp 320°C, Lit.[27] mp 342–345°C).

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$RCONHCH_2OH \rightarrow RCONHCH_2OPCl_2 \rightarrow RCONHCH_2{-}P(O)Cl_2 \rightarrow$ **3**.
We assume that the reaction is a *P*-amidomethylation reaction with generation of *N*-acyliminium ion as the crucial step:
$RCONHCH_2OH \rightarrow RCONHCH_2^+ \leftrightarrow RCONH{=}CH_2$
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